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Multiple neonatal endocrinopathies in McCune–Albright syndrome

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Abstract: Two cases of McCune–Albright syndrome (MAS) are reported who presented in the neonatal period with profound failure to thrive, cardio-respiratory distress, precocious puberty and Cushing's syndrome for which both underwent bilateral adrenalectomy. Both girls had also bilateral nephrocalcinosis; in one case that may have been attributed to Cushing's syndrome, but in the second case the cause remained obscure with no obvious abnormality of calcium metabolism. The first girl had hydrocephalus which is uncommon in this condition and the second girl still failed to thrive at the age of 6 years, despite adequate caloric intake and hormonal manipulation. A constellation of other abnormal features are described. These cases illustrate the complexity of MAS which can become a life-threatening or a debilitating disorder.

Key words: Cushing's syndrome; failure to thrive; hydrocephalus; McCune–Albright syndrome; nephrocalcinosis.

McCune–Albright syndrome (MAS) is a sporadic disease characterized by polyostotic fibrous dysplasia, *café au lait* spots and a variable association of hyperfunctional endocrinopathies.[1,2] The disorder is caused by a mutation in the gene for the alpha subunit of the stimulatory G-protein which brings about permanent activation of the tissues stimulated through receptors coupled to the G-protein-cAMP protein-kinase A dependent pathway.[3] The clinical picture is extremely variable among affected individuals and is consistent with a postzygotic somatic mutational event resulting in a mosaic distribution of the mutation.[4,5] Affected endocrine tissues include gonads, thyroid, parathyroid, adrenal cortex and pituitary somatotrophs. A multiplicity of non-endocrine abnormalities have been described in the literature, including the occurrence of unexplained sudden death.[6,7]

Severe neonatal presentation of MAS is rare. We report two cases of MAS, who presented shortly after birth with Cushing's syndrome, necessitating bilateral adrenalectomy. Many other abnormal features were associated with the autonomous adrenal hyperplasia.

CASE 1

The first girl was initially referred at 5 months of age to a respiratory unit due to her respiratory distress. She had been diagnosed as having achondroplasia on the basis of dysmorphic features (large forehead, small nose, flat nasal bridge and short limbs). On admission, she was very short (height SDS, 7.9) and underweight (3.2 kg). Her blood pressure was elevated (110/70 mmHg). She had marked developmental delay. Large pigmented skin patches over the right side of her abdomen and legs were noted. Breast enlargement [B3] bilaterally and a bulging fontanelle were also present.

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Investigations

Investigations showed hypercortisolism with a loss of diurnal rhythm (1116 nmol/L, 0.800 h; normal range (NR) 140–700; 1057 nmol/L, 24.00 h; NR, < 140) and no suppression on high dose dexamethasone (1037 nmol/L). The diagnosis of precocious puberty was radiologically supported by pelvic ultrasound findings (enlarged uterus for age and an ovarian cyst of 6.2 cm) and its peripheral origin was biochemically confirmed by high oestradiol level (491 pmol/L; NR, 7–37) associated with prepubertal levels of gonadotrophins. The girl's liver function was altered, with an elevated level of aspartate transaminase (AST) (111 U/L; NR, 35–55) but with no associated cholestasis. The renal ultrasound revealed bilateral nephrocalcinosis. Her serum phosphate levels were slightly below normal values (0.9 mmol/L; NR, 0.9–1.38) but normal tubular reabsorption of phosphate (TRP) values were reported (92%; NR, 80–100). However, serum calcium concentrations remained within normal range limits, as did parathyroid hormone (PTH) concentrations and renal function. A skeletal survey revealed a generalized reduction of bone density with particular sclerotic areas in the vertebral bodies, proximal phalanges and distal metacarpals. A cranial computed tomography (CT) scan showed enlargement of the lateral and third ventricles consistent with hydrocephalus but there was no evidence of raised intracranial pressure. The echocardiogram was reported as normal. Respiratory distress was found to be due to a combination of infective cause and a high cardiac output related to her hypercortisolism. The association of skin pigmentation, bone lesions, nonpituitary dependent Cushing's syndrome and gonadotrophin-independent precocious puberty led to the diagnosis of MAS.

Outcome

The girl underwent bilateral adrenalectomy at 8 months of age which was followed by a rapid recovery. She commenced hydrocortisone and fludrocortisone replacement. In order to arrest her precocious puberty (characterized by frequent episodes of vaginal bleeding), cyproterone acetate was commenced at the

age of 26 months. Excessive bone age advancement (2.5 years) had occurred by that time. Despite treatment, and possibly due to lack of compliance, her precocious puberty was not well controlled (Table 1). Investigations excluded the onset of gonadotrophin-dependent puberty. At the age of 3 years she developed thyrotoxicosis with a small goitre (thyroid stimulating hormone (TSH) < 0.1 mU/L; NR, 0.5–6.0; free-T_4: 34.2 pmol/L; NR 9.1–23.8; free-T_3: 19.7 pmol/L; NR 2.5–8.2). She was, therefore, commenced on carbimazole 10 mg three times a day. Her hydrocephalus did not increase and her nephrocalcinosis has shown recent signs on ultrasound of regression. Her AST levels diminished gradually, albeit remaining at the higher normal range (Table 1). After the age of 2 years, the girl's growth velocity accelerated, producing gradual growth catch up. Her height reached the tenth percentile at the age of 4 years, and the 25th percentile at the age of 5 years. At the same time, her weight gain showed significant improvement. The dysplastic bone lesions have progressed, causing severe deformities.

CASE 2

The second girl was referred to our centre at the age of 11 weeks for failure to thrive. Since birth, she had been suffering from diarrhoea and poor feeding. At 7 weeks of age she had been admitted to a surgical unit for treatment of a right inguinal hernia repair when multiloculated bilateral ovarian cysts were discovered and drained.

On admission the girl was Cushingoid in appearance. She had hepatomegaly, large masses palpable bilaterally in the lower abdomen and prominent labia minora. Large *café au lait* spots were noted on her left cheek, upper back and sacrum. She weighed 2 kg and was hypertensive (125/90 mmHg).

Investigations

Endocrine investigations confirmed the presence of Cushing's syndrome with high serum cortisol levels not suppressible by high-dose dexamethasone (basal cortisol 09.00 h, 1462 nmol/L; NR, 140–700; 24.00 h, 1420 nmol/L; NR, < 140). Cortisol levels after 3 day high-dose dexamethasone were 09.00 h, 1600 nmol/L; 24.00 h, 1566 nmol/L). High oestradiol levels (12 000 pmol/L; NR, 7–37) associated with low gonadotrophins (leutinising hormone (LH) < 0.5 IU/L; follicular stimulating hormone (FSH) < 0.5 IU/L), taken together with ultrasound and clinical findings, confirmed the diagnosis of gonadotrophin independent precocious puberty.

An abdominal ultrasound revealed the presence of bilateral nephrocalcinosis, but plasma calcium, plasma phosphate and renal function remained within normal limits for the age. Intact PTH concentration was normal at 21 ng/L (NR, 5–45). Her liver function tests showed high AST levels (719 U/L; NR, 35–55) but no cholestasis. A skeletal survey demonstrated abnormal bone texture in the iliac crest and the metadiaphyseal regions of both femurs, right tibia and left distal radius. She underwent bilateral adrenalectomy. Postoperatively, she had severe episodes of respiratory distress with infiltrates evident on chest X-ray necessitating oxygen and Frusemide 2 mg/kg.

Outcome

Despite the removal of her adrenals, the girl continued to have evidence of endogenous cortisol and aldosterone production (08.00 h cortisol level 1 month postoperatively when being administered dexamethasone, 148 nmol/L; aldosterone levels approximately 500 pmol/L; NR, 200–1000). The source of her cortisol and aldosterone production was unclear and an iodocholesterol scan failed to reveal any functional adrenal tissue. She was commenced on hydrocortisone and fludrocortisone replacement therapy. After her operation, the patient remained hypertensive and it was only after several weeks that she could be weaned off all anti-hypertensive medication. Signs of Cushing's syndrome gradually resolved over 3 months. Like the previous patient, the control of her precocious puberty was not complete despite administration of cyproterone acetate. Investigations have ruled out associated central puberty.

At the age of 3 years the girl developed occult T_3 thyrotoxicosis (free-T_3, 9.2 pmol/L; NR, 2.5–8.2; free-T_4, 18.3 pmol/L; NR, 9.1–23.8; thyrotrophin releasing hormone test, basal TSH < 0.1 mU/L 20 min; 1.2 mU/L 60 min; 0.1 mU/L; NR, 0.5–6.0). There was no evidence of goitre on ultrasound and she was commenced on continuous carbimazole.

Persistent failure to thrive remained a major concern during follow-up. She remained predominantly fed by nasogastric tube. Despite adequate hormonal replacement, her growth failed to accelerate or catch up. The girl's overall development remained delayed. Her polyostotic fibrous dysplasia caused several bone

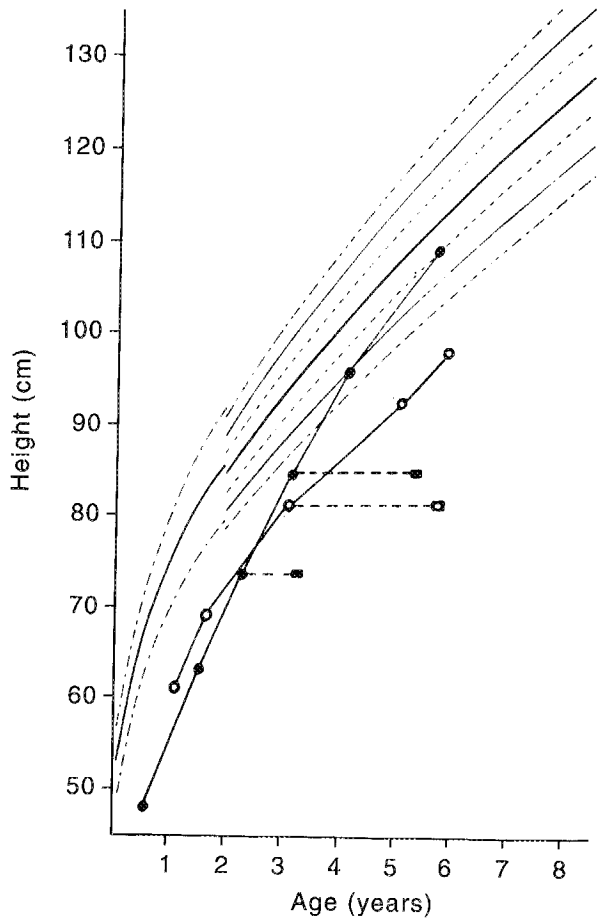

Fig. 1 Growth data for two girls with McCune–Albright syndrome. (●), patient 1: (○), patient 2; (■), bone age of patient 1; (□), bone age of patient 2.

	Gonadal axis (NR: FSH/, LH*, E_2, 7–37)	Thyroid function (NR: TSH, 0.5–6.0; Free T_4, 9.1–23.8: Free T_3, 2.5–8.2)	Cortisol (NR: 08.00 h, 140–700; 24.00 h, < 140)	Liver function (NR: AST, 35–55; total bilirubin: < 18)	Calcium (Ca) phosphate (PO_4) NR: Ca, 2.22–2.58; PO_4, 0.9–1.38)	Alkaline phosphatase (NR: 110–440 U/L)	Creatinine (NR: < 102)	Urinary phosphate TRP (NR: 80–100%)
Case 1	5 months FSH < 0.5 IU/L LH < 0.5 IU/L E_2 491 pmol/L		Presentation 08.00 h 1.116 nmol/L 24.00 h 1.057 nmol/L	Presentation AST 122 U/L Bilirubin < 12 µmol/L	Presentation Ca 2.36 mmol/L PO_4 0.9 mmol/L	Presentation 614 U/L	Presentation 11 µmol/L	Presentation 7.8 mol/L 92%
	1.5 years FSH < 0.5 IU/L LH < 0.5 IU/L E_2 < 20 pmol/L			1.5 years AST 55 U/L				
		3 years TSH < 0.1 mU/L free T_4 34.2 pmol/L free T_3 19.7 pmol/L			3 years Ca 2.49 mmol/L PO_4 1.5 mmol/L	3 years 263 U/L	3 years 30 µmol/L	3 years 19 mmol/L 91%
	5 years FSH < 0.5 IU/L LH < 0.5 IU/L E_2 492 pmol/L			5 years AST 77U/L				
Case 2	11 weeks FSH < 0.5 IU/L LH < 5 IU/L E_2 12 000 pmol/L		Presentation 08.00 h 1462 nmol/L 24.00 h 1420 nmol/L	Presentation AST 719 U/L Bilirubin 16 µmol/L	Presentation Ca 2.64 mmol/L PO_4 1.28 mmol/L	Presentation 592 U/L	Presentation 27 µmol/L	Presentation 10 mmol/L 90%
	1 year FSH < 0.5 IU/L LH < 0.5 IU/L E_2 1046 pmol/L			1.5 years AST 120 U/L Bilirubin 7 µmol/L				
		3 years TSH < 0.1 mU/L free T_4 18.3 pmol/L free T_3 9.2 pmol/L			3 years Ca 2.55 mmol/L PO_4 1.27 mmol/L		3 years 30 µmol/L	3 years 14.75 mmol/L 87%
	5.1 years FSH < 0.5 IU/L LH < 0.5 IU/L E_2 40 pmol/L			6 years AST 42 IU/L	6 years Ca 2.52 mmol/L PO_4 1.17 mmol/L	6 years 525 U/L	6 years 35 µmol/L	6 years 12.72 mmol/L 93%

FSH, follicular stimulating hormone; LH, leutinising hormone; TSH, thyroid stimulating hormone; AST, aspartate transaminase; NR, normal range. *NR FSH/LH: 0–12 months: 0.1–11/0.08–8; 1–2 years: 0.7–6.7/0.03–3.9; 4–6 years: 1.0–7.4/0.5–15.

fractures (left knee and both femurs). She has never been able to walk. Apart from generalized osteopenia there was no evidence of active rickets, however her nephrocalcinosis has not shown signs of regression according to ultrasound examination. Her AST levels diminished but remained slightly elevated until recently. Other parameters of liver function have always been normal. Currently, the main concerns remain failure to thrive, global developmental delay, and crippling fractures.

DISCUSSION

The two cases presented illustrate the complexity of managing MAS, which requires a multidisciplinary approach. The onset of MAS during infancy is rare and when it does occur in infancy, several weeks or months may elapse before correct diagnosis is made. Neonatal forms of MAS can be fatal and may manifest by profound growth failure, developmental delay, failure to thrive and cardio-respiratory distress.[6] None of these manifestations is pathognomonic of the condition. Skin lesions suggestive of the condition do not appear before the first month of life. Non-endocrine involvement (in addition to bone and skin) is not rare and can be either a direct expression of the disease or an indirect consequence of hormonal imbalance.[8] Shenker *et al.*[6] hypothesized that severe disease may be related to an earlier mutational event leading to more widespread distribution of mutant cells. However, multiple endocrine abnormalities should alert the clinician to the possible presence of MAS.

The diagnosis of MAS can be confirmed by documenting the GSα mutation in affected tissues. Unfortunately, the adrenal glands of our two patients were not retained for further molecular studies. Nevertheless, there was overwhelming clinical evidence that these two girls were affected by MAS.

One striking feature of our first girl was the presence of arrested hydrocephalus. Although other neurodevelopmental abnormalities associated with MAS have been described,[9] hydrocephalus has not been previously reported as associated with this condition and its relationship to MAS is unknown.

Hyperparathyroidism and hypophosphataemic rickets are two well-recognised manifestations of MAS.[10,11] Nephrocalcinosis is a frequent consequence of hyperparathyroidism, but the latter seems unlikely in our two cases in view of their normal serum calcium and PTH values. Nevertheless, phosphate values and tubular reabsorption of phosphate were relatively low in the first girl and urine phosphate concentrations were high in the second girl which may have indicated occult hyperparathyroidism. There were no X-ray features typical of hypophophataemic rickets. Nephrocalcinosis in this disorder is usually related to treatment with vitamin D.[12] Therefore, in the first case, the most probable explanation for nephrocalcinosis remains Cushing's syndrome[13] and the subsequent regression of nephrocalcinosis appears to corroborate this hypothesis. In the second case, no clear explanation could account for nephrocalcinosis. High levels of transaminases (two to seven-fold above the upper limit of the normal range) found in our patients may indicate associated transitory hepatitis; however, in contrast to other cases described in the literature, no sign of cholestasis could be documented. Liver biopsies were not performed in view of subsequent improvement in our two patients' biochemical parameters.

A diagnosis of MAS should be considered when a neonate presents with Cushing's syndrome and precocious puberty with large asymmetric cystic ovaries. However, the difficulty of diagnosis in a neonate may be increased in the absence of characteristic skin signs or skeletal lesions.

Conclusion

The two cases presented emphasize the broad range of abnormalities in MAS. When neonatal manifestations are misleading, the sequelae may become life threatening. The general paediatrician should be aware of the possibility of MAS in a sick neonate with Cushing's syndrome and/or gonadotrophin independent puberty in the absence of the typical hyperpigmented spots. The latter does not usually appear until 6 weeks of age.

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